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Commentary

Science and Politics: The Possible Regulation of Cancer Promoters

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To address the problems associated with the regulation of tumor promoters, one must recognize that a regulatory agency's actions in the formulation of policy redound from a matrix of political, social and scientific pressures; each affecting the other, and all influencing the final policy outcome. Scientific understanding of the mechanism(s) of tumor promotion plays a determinant role in such interaction, for the selection of particular biological tests as surrogates for human response to chemical exposure provides the radical upon which such interaction occurs, industry responding to the legal, regulatory instrument that relies in turn on scientific confidence in required tests. These parties operate within the penumbra cast by political expedients, environmental action groups, and special interest lobbies whose concerns involve the cost of testing, the availability of resources, the consideration of particular chemicals of economic or symbolic value, and other such aspects of regulatory policy or its consequence. In examining the complex development of policy for future regulation of tumor promoters, we must attend first to the legal instrument framing such regulations, assessing probable impact on these various scientific, economic, social and political factors.

Potential regulation of most tumor promoters would fall within the regulatory ambit of the U.S. Environmental Protection Agency, specifically the Toxic Substances Control Act of 1976 (TSCA). As with other regulatory acts, the making of public policy, in this case concerning the manufacture and use of chemicals, derives from two major concerns: the attempt to achieve technical analyses of risks and benefits as one base for regulation, and a general judgment of social welfare or public safety as the other.

Technical analysis and social judgment entwine at the outset of TSCA, the Congress finding risk of injury to health and environment from chemical exposure (*1*), and then establishing as United States policy the development of adequate data regarding the effect of chemical substances and mixtures on health and the environment in order to preclude risk of injury by restrictions on manufacture and use. Social judgment, basically a political process, was intended to lie with the Congress, while technical analysis was to lie with the administrator of the regulatory agency. This basic concept has failed due to continued inexactitude of scientific risk assessment, forcing technical assessment processes to become quasi-political, dependent upon convention, upon opinion and to a surprisingly large degree upon social judgment within the agency and from without. The U.S Environmental Protection Agency, however, by its nature—and especially as that nature is formed under TSCA—is a poor instrument for making or attempting to make social judgment. The continued misperception of the EPA as an instrument solely for technical assessment is then a mistake, and although scientific truth is supposed to underly and to shape the decisions that agency renders, the uncertainty in scientific risk assessment continues to be so great that the regulatory processes must be considered principally political judgment rather than technical analysis. One need only consider the posture assumed by the present administration compared to that of its predecessor to see that the same scientific facts regarding the regulation of specific environmental agents can be used to assume two largely opposite stances; the scientific facts remaining unchanged, political perspective changing.

Concerning possible regulation of tumor promoters by EPA, the proportion of scientific fact vis-

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a-vis political judgment can best be understood by such an illustration as the following. If most scientists, upon evaluation of any test results presented to them, would reach generally the same appreciation as to degree of risk an agent proffers, then judgment would play a lesser role. On the other hand, it is clear that the opposite condition generally applies for evaluating potential carcinogens, especially tumor promoters. It seems clearly evident from the papers presented at this conference, for example, that neither is there agreement for a biological basis for tumor promotion, nor is there statistical correlation between tests for tumor promotion in laboratory animals and the human experience. Political judgment, then, plays a major part in the potential regulation of tumor promoters. The degree of social judgment-making versus technical analysis going into regulatory decisions is determined in large part by the regulatory instrument under which the administrator operates. The Food, Drug and Cosmetic Act as amended in 1958 stands in polar opposition, in this regard, to TSCA.

Surely the best known example of congressional exercise of social judgment relative to regulation is the Delaney anti-cancer clause attached in 1958 to the Food, Drug and Cosmetic Act prohibiting use of any food additive determined to be carcinogenic in animal or in man (*2*). Although a great deal of discussion continues to surround this legislative action, the nature of the amendment, its simplicity and rigidity, takes the inherent uncertainty of technical analysis out of the administrative domain, and also makes a clear determination as to risk; no risk being acceptable. The Delaney principle, thus, obviates the problems associated with uncertainty in risk versus benefit analysis of carcinogens. Since the basis of such an amendment to regulation lies in congressional social judgment-making, only congressional exception can be made for carcinogens demonstrating benefit, e.g., the case of saccharin.

TSCA provides no posture similar to that fostered by the Delaney principle. The policy established in Section 2 of the act is one of regulating "chemical substances and mixtures which present an unreasonable risk of injury to health or the environment; the administrator being charged with evaluating risk versus benefit of chemical exposure creating possibility of "serious or widespread harm to human beings." The administrator's determination of acceptable risk, a technical analysis occurring within the economic-politico-social judgment matrix, ultimately assumes an acceptable scientific data base. Whatever the arguments for or against congressional social judgment-making that results in actions such as the Delaney principle, the President's Scientific Advisory Committee Panel on Chemicals and Health notes "that it seems to be the very lack of information plus an implied threat ... which has led Congress to take social judgment-making into their own hands" (*3*). The implications for TSCA regulation of tumor promoters rest in the inherent assumption of that act that conclusive scientific data can drive administrative decision-making toward that goal.

The problems of regulating any chemical based on one or more scientific tests is one of answering two questions concerning surrogation. The first question is whether the test employed is an appropriate surrogate for exposed human populations, that is, to ask whether the biology of the effect measured is a surrogate for the pathogenic process in human beings. The second, and the more important, question is to ask whether the test is predictive of human hazard; the answer to this question being a statistical association independent of theoretical biological considerations. An approach to these two questions is illustrated best by considering a widely used test for prediction of potential carcinogenic hazard, the Ames assay.

The Ames assay, measuring mutation in bacteria, has been accepted and is widely used due to two factors. First, the test measures an endpoint believed to be germane to cancer, i.e., mutation. It may be that mutation *per se* is not the cancer-initiating event; indeed recently some have speculated that other events, for example the induction of transposition of genetic elements, could be the critical event. But in the continued use of the Ames assay, the fact that the exact endpoint may not be the most critical event is not a disqualifying factor due to a second and more important fact that for the Ames assay, whatever the endpoint measured, the predictive value is high (*4*). Agents that produce mutation in the Ames test tend to produce cancer in animals, and agents that produce cancer in animals tend to produce cancer in man. This direct theme, though imperfect in many specific examples, is strong enough to override caveats and objections that the various extrapolations for specific chemicals are flawed. To approach the same questions for predicting the potential human hazard from tumor promoters is immensely more difficult, not only from the viewpoint that there is little agreement on the critical biological action of tumor promoters, but also due to an almost complete absence of human data on which to base extrapolations for the few tests now used to evaluate potential human hazard.

The exact biological basis for cancer promotion is not known. Tumor promoters are usually defined operationally as agents given subsequent to "cancer initiators" in selected animal systems that increase the incidence of tumors or accelerate their appear-

ance. The search for the critical molecular and cellular event(s) in promotion has been intensive and has led to a compendium of effects produced *in vivo* and *in vitro* by archetypal promoters such as TPA. Most scientists, however, would agree in general with Farber who summarizes "at present it is impossible to relate the findings *in vitro* to chemical carcinogenesis *in vivo*" (*5*). Thus deprived of knowledge of the critical event, it is impossible to attempt to extrapolate from surrogate test systems to potential human hazard on the basis of common molecular or cellular etiology.

The second question, that of confidence in extrapolation based on statistical associations from the outcome of "promoter" tests to known promotion of human cancer, cannot be answered at all; there is no human cancer data that can be clearly ascribed to the act of a promoter. Clearly, there are several examples of synergism between carcinogens that elevate human cancer rates, but none of these carcinogens can be classified solely as a cancer promoter. As an example of such synergism, consider the interaction in psoriatics treated with x-rays and subsequently with oral psoralen and long-wavelength ultraviolet light (PUVA therapy). Stern et al., observed that such patients who had experienced x-ray treatment even 5 years or more before PUVA, evidenced elevated incidence of squamous cell carcinomas (*6*). PUVA therapy is a mutagenic treatment in the Ames test and other simple systems, so it is difficult to interpret these human data in terms of initiators or promoters despite the clear synergism. This clearly illustrates in a specific way the more general problem of applying a simple initiator-promoter scheme to human carcinogenesis produced by multiple and sequential exposures. It seems much more useful to consider this simple dichotomy as a subclass of interactive carcinogens, perhaps a very rare subclass.

Even if these formidable scientific problems of technical assessment of tumor promoters could be solved, regulation under TSCA is by its nature a lengthy and complicated task, even for consideration of known human carcinogens. Table 1 lists all specific chemicals or agents regulated by the U.S. EPA under TSCA from the act's inception in 1976 through October 1981. Asbestos, for an example, has long been known to be a human carcinogen, and the fact that it has not yet been regulated in a final manner illustrates most clearly that even an agent for which conclusive and scientifically sound data exist as to its hazard for exposed human beings, political debate comparing potential social benefit with the degree of hazard can retard and even stop regulation.

Thus it seems that there is no rigorous scientific system of tests that will permit a meaningful prediction of human hazard from tests of a potential cancer promoter. If the promoter alone can produce cancer in the long-term, whole animal bioassay, then indeed it could, like any other carcinogen, be evaluated by standard techniques. On the other hand, if the agent will only produce increased cancer incidence after treatment with an "initiator," the laboratory scientist is hard put to devise an animal model that could be a surrogate for an "initiated" general human population. Lacking such an animal system that would be acceptable through some degree of scientific consensus to represent "initiated" human populations in a meaningful way, it is difficult to imagine the extrapolation from any other system to human hazard.

In summary, it appears that no acceptable data base exists that will permit even the smallest amount of confidence for the extrapolation from any system now used to measure promotion to the predicting of potential human hazard from cancer induction. That is not to say that TPA, for instance, could not be regulated, but it does say that even for this well tested agent the regulatory decision would

Table 1. Chemicals regulated by the U.S. Environmental Protection Agency under TSCA (1976–1981).

Chemical	Type of test data available	Action taken
Chlorofluorcarbons (CFC)	Depletion of ozone layer; implied increase in human skin cancer	Prohibition of aerosol use (3/17/78)
Polychlorinated biphenyls (PCB)	Animal carcinogen; accumulation in human beings and the environment	Banned (5/31/79)
Asbestos	Human carcinogen	Proposed commercial use restriction; no final action
TCDD	In animals; acute toxicity and reproductive toxicity; carcinogenesis; suggestion of reproductive toxicity and cancer in human	Restriction on storage and disposal of waste (5/19/80)
Polybrominated biphenyls (PBB)	Animal reproductive toxicity; mutagenicity	Required notification of manufacture or import (10/24/80)
Seven new chemicals	Varied low level tests	Additional testing requested; chemicals withdrawn

be one of establishing policy based on general concepts, not on rigorous extrapolation from well defined and predictive test systems. This in turn means that a new chemical for which there is no *a priori* reason to believe to be a cancer promoter would probably not be tested in multiple, short-term bioassays now used. Even if such a chemical were so tested, and produced positive results, it is unlikely that the U.S. Environmental Protection Agency under TSCA would or could take regulatory action that could successfully withstand legal challenge.

In conclusion, it seems best to state that current scientific knowledge and testing technology does not permit the prediction of human hazard of a given, putative cancer promoter with any degree of rigor. The absence of scientific rigor implies in turn that politics in both the smaller and larger sense will determine whether any promoter can be or will be regulated. Thus the question is not whether any scheme, scientific or political, produces a prediction of hazard, but whether that prediction has any useful application to human carcinogenesis. For those who propose that certain extant testing schemes can or will predict human carcinogenic hazard, we must be like Hotspur in the first part of *Henry IV* who, upon hearing Glendower brag that "I can call spirits from the vasty deep," replied "Why so can I or so can any man/ But will they come when you do call them."

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